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(54) Title: NITRATE ESTER DERIVATIVES USEFUL FOR PREPARING DRUGS FOR EPILEPSY

(57) Abstract: Nitrooxyderivative compounds or salts thereof having the following general formula (I): $A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2$ (I) wherein: c0 is an integer and is 0 or 1, b0 is an integer and is 0 or 1, $A = R\text{-}T_1\text{-}$, wherein R is the radical of formula (II) as defined in the application; B is such that its precursor is selected from aminoacids, hydroxyacids, polyalcohols, compounds containing at least one acid acid function, C is a bivalent radical containing an aliphatic, heterocyclic or aromatic radical.

NITRATE ESTER DERIVATIVES USEFUL FOR PREPARING DRUGS FOR EPILEPSY

* * * * *

The present invention relates to drugs for the epilepsy treatment.

Epilepsy is defined as a group of cerebral disorders which appear with sudden and transitory episodes (fits or attacks) of abnormal phenomena having a motor origin (convulsions). The epileptic fits are characterized by patient consciousness loss and often accompanied by convulsions which in the most serious cases are extended to the musculature of the whole body.

Epilepsy has a high incidence in the population, only in the United States patients are 2.5 millions and every year about 100,000 new cases are diagnosed.

A classification of said disease based on clinical symptoms of the epileptic fits and on the state of the encephalographic trace is the following:

1) Partial fits (simple, complex or partially generalized) which appear with convulsions limited to only one limb or to a group of muscles; generally there is not consciousness loss even though in some cases (complex partial fits) episodes of confused behaviour appear.

2) Generalized fits which appear with consciousness loss episodes (epileptic absences) which can be accompanied by isolated clonic contractions (myoclonic fits), contractions of all the muscles, (clonic fits), generalized convulsions (tonic-clonic fits).

Epilepsy represents a serious social problem since this disease affects both the patient social relations and the working efficiency; in young people epilepsy influences not

only their insertion in the social organization but also the school efficiency.

Epilepsy is above all a serious sanitary problem: infact patients must take drugs for long periods (the therapy must be continued at least for two years after the fit disappearance). The drugs at present used, such for example phenobarbital, phenytoin, carbamazepine, in some patients are not able to control the convulsive activity and can interact with other drugs and, besides, cause side effects such as headache, nausea, vomit, sedation.

The need was felt to have available drugs for the epilepsy treatment effective in reducing the incidence and/or the seriousness of convulsive fits and having lower side effects.

It has now been surprisingly and unexpectedly found that said technical problem can be solved with the class of drugs which is described hereunder.

An object of the present invention are nitrooxyderivative compounds or salts thereof having the following general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

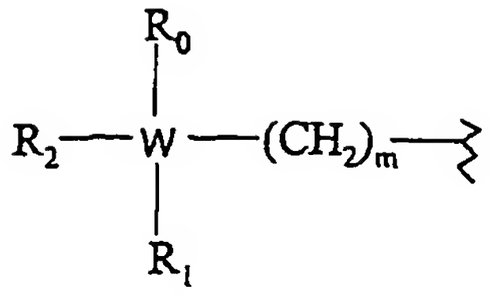
wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = R-T_1-, wherein

R is the radical of a precursor drug, having formula II:



(II)

wherein:

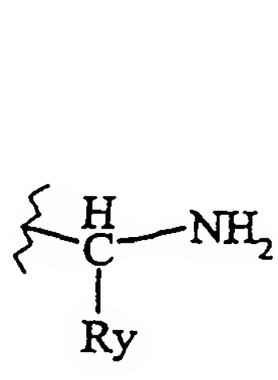
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

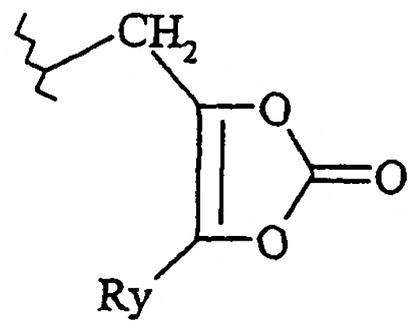
R_0 = H, $-(CH_2)_n-NHR_{1A}$, n being an integer from 0 to 2, wherein

R_{1A} = H, $-C(O)-R_{1H}$, $-C(O)O-R_{1H}$, wherein

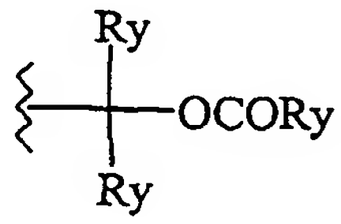
R_{1H} is a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



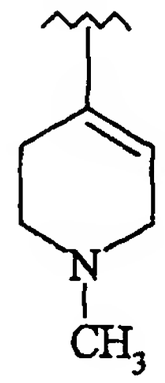
(II-B)



(II-C)



(II-D)



(II-E)

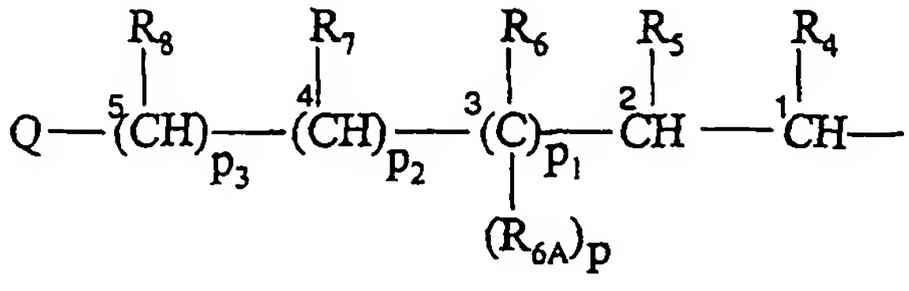
wherein Ry is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

R_1 = H, when W = N, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- mono- or di-hydroxy substituted benzyl, preferably 3-4 di-hydroxy substituted;
- amidino group: $H_2N(C=NH)-$;

the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

wherein:

p, p_1, p_2 are integers, equal to or different from each other and ar 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1-C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1-C_6 alkyl,
- C_3-C_6 cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:
  - linear or branched C_1-C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
  - phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_{6A} = H, methyl;

R_6, R_{6A}, R_7, R_8, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type is present, between C_1 and C_2, R_4 and R_5 are free valences such as to form the double bond between C_1 and C_2; when the unsaturation is between C_3 and C_4, R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4; when the unsaturation is between C_4 and C_5, R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups:

$-OCH_3$, $-CF_3$, nitro; or Q can have one of the following meanings:

- C_3-C_6 cycloalkyl
- linear or branched C_1-C_6 alkyl
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) R_2 with R_1 and with W = C taken together form a C_4-C_{10}, preferably C_6 saturated or unsaturated, preferably saturated ring;

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1C}, R_{1C} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

$B = -T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B = (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI} = $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B $-T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with $-N(Z^I)(Z^{II})$, being:

- Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible,
- Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined is preferably selected in the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetylpenicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, slected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic alcohols, selected from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethyl alcohol, coniferyl alcohol, allopurinol;

- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein:

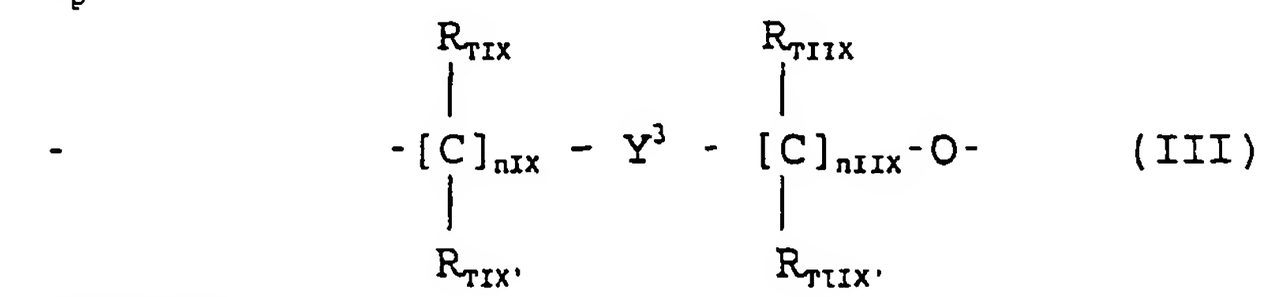
when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

when b0 = 0 : T_c = (CO) when t = 0, T_c = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, T_{BI} = X = —O—;

Y has one of the following meanings:

Y_p :



(III)

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from one to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected among nitrogen, oxygen, sulphur;

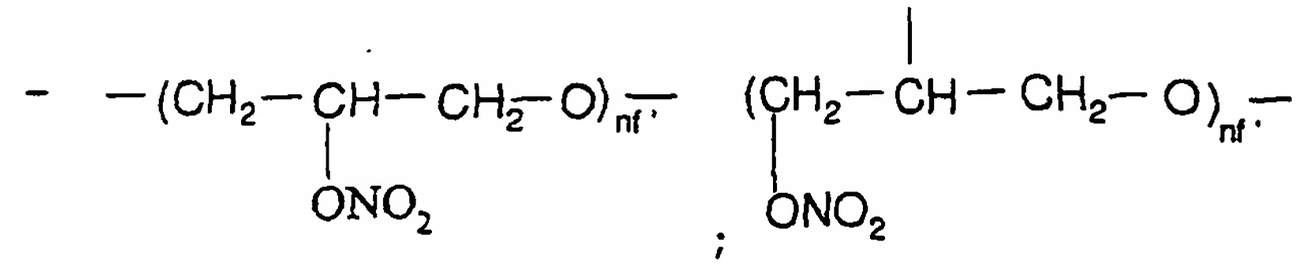
or Y can be:

Y_0, selected from the following:

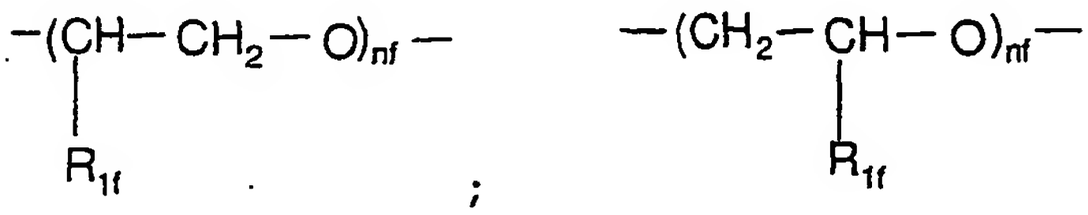
- an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from

5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:



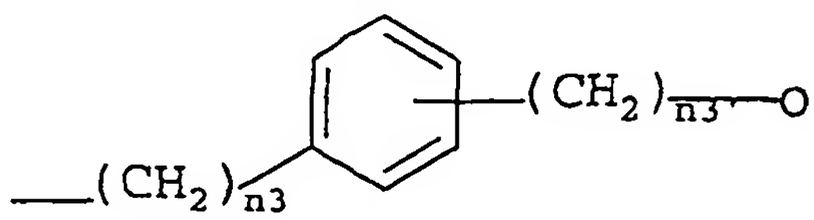
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;



wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 2 to 4;

- Y_{AR}, selected from:

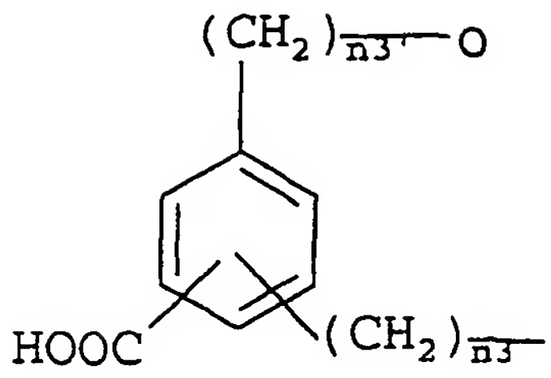
  Y_{AR1}:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

- Y_{AR2}:



(VI)

wherein n3 and n3' have the above meaning.

When in formula (II) W = C, m = 1 and R_0 = $-(CH_2)_n-NH_2$ with n = 1, R_2 and R_1 with W as above form together the cyclohexane ring, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;

when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;

when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;

when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the thioguanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;